

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 39/00	A2	(11) International Publication Number: WO 98/39026 (43) International Publication Date: 11 September 1998 (11.09.98)
(21) International Application Number: PCT/US97/24133 (22) International Filing Date: 31 December 1997 (31.12.97) (30) Priority Data: 60/040,154 7 March 1997 (07.03.97) US (71) Applicant (for all designated States except US): BIOGEN, INC. [US/US]; 14 Cambridge Center, Cambridge, MA 02142 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): KALLED, Susan, L. [US/US]; 2E Brewer Street, Jamaica Plain, MA 02130 (US). THOMAS, David, W. [US/US]; 9 Upland Road, Wellesley, MA 02182 (US). (74) Agent: FLYNN, Kerry, A.; Biogen, Inc., 14 Cambridge Center, Cambridge, MA 02142 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>Without international search report and to be republished upon receipt of that report.</i>
(54) Title: METHODS OF THERAPEUTIC ADMINISTRATION OF ANTI-CD40L COMPOUNDS (57) Abstract Immune-related disorders can be effectively treated by administering anti-CD40L compounds at intervals of three weeks or more.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

METHODS OF THERAPEUTIC ADMINISTRATION OF ANTI-CD40L COMPOUNDS

5

Field of the Invention

The invention relates to regimens for therapeutically administering anti-CD40L compounds to patients.

10 **Background of the Invention**

One of the necessary reactions in the generation of antibodies is the interaction of CD40 on B cells with CD40 ligand (CD40L) on activated T cells, a step which is required for B cell growth and subsequent production of antibodies. (Note: "gp39" is used synonymously for CD40L in some reports.) As further described below, a number of anti-CD40L
15 compounds have been produced, and some have been tested in animals for efficacy in altering the course of antibody-associated diseases.

The protocols used in the reported experiments on effects of anti-CD40L compounds on animals with immune disorders have employed doses of the compounds administered to the animals at intervals of two weeks or less, with typical intervals between treatments being 1-7
20 days. (See, e.g., Mohan et al., J. Immunol. 154: 1470-1480, 1995; Early et al., J. Immunol. 157: 3159-3164, 1996; Stüber et al., J. Exp. Med. 183:693-698, 1996; Chen et al., J. Immunol. 155:2833-2840, 1995; Gerritse et al., Proc. Natl. Acad. Sci. 93:2499-2504, 1996; Green et al., T. Virol. 70:2569-2575, 1996; Durie et al., Science 261:1328-1330, 1993; Durie et al., J. Clin. Invest. 94:1333-1338, 1994; Larsen et al., Transplantation 61:4-9, 1996;
25 and Griggs et al., J. Exp. Med 183:801-810, 1996). There has been no available information that suggests that less frequent administration of anti-CD40L compounds would be efficacious in inhibiting the production of pathologic antibodies or improving the course of immune-related diseases.

Summary of the Invention

30 The inventors have demonstrated that administering an anti-CD40L compound at intervals of three weeks or more is effective in treatment of disorders with antibody-related

-2-

pathogenesis. The invention provides a method of treating a patient with an antibody-related disease, which includes administering a therapeutically effective amount of an anti-CD40L compound to the patient on a first day and again on a second day, with at least about 3 weeks between the first day and the second day. Similar amounts of an anti-CD40L compound may subsequently be given to the patient, with at least about 3 weeks between successive doses. In one embodiment, the interval between doses is at least about 4 weeks.

In another aspect of the invention, a method is taught for treating a patient with an antibody-related disease, comprising administering a therapeutically effective amount of an anti-CD40L compound to the patient for a first therapeutic period at intervals of less than about 3 weeks, then administering a therapeutically effective amount of an anti-CD40L compound to the patient for a second therapeutic period at intervals of at least about 3 weeks or at least about 4 weeks.

A further application for the above-described administration regimens is for treating a patient with a chronic immune system disorder, such as psoriasis, allergic conditions, arthritis or multiple sclerosis.

In another embodiment, the methods of the invention are useful for treating a chronic autoimmune disease, such as systemic lupus erythematosus, myasthenia gravis, autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, or anti-phospholipid syndrome.

Yet another aspect of the invention provides a method of inhibiting rejection of transplanted tissue within a patient; this method includes administering a therapeutically effective amount of an anti-CD40L compound to the patient on a first day and again on a second day, with at least about 3 weeks between the first day and the second day. The compound may be given subsequently at varying intervals, but in one embodiment, it is given subsequent to the second dose at intervals of at least about 3 weeks or at least about 4 weeks. The transplanted tissue may be any organ or tissue which is suitable for transplantation. Particularly intended for inclusion are transplants of skin, kidney, liver, heart, bone marrow, or eye tissue. The graft may be an allograft or a xenograft.

The methods of the invention may also be useful in suppressing immune reaction after gene therapy.

-3-

In an alternative dosing regimen for inhibiting rejection of transplanted tissue within a patient, an anti-CD40L compound is administered to the patient for a first therapeutic period at intervals of less than about 3 weeks, then administering for a second therapeutic period at intervals of at least about 3 weeks.

5 The anti-CD40L compound may be any compound that binds to CD40L on the surface of CD40L-expressing cells, such as activated T cells. In one embodiment, the compound is an anti-CD40L antibody, preferably a monoclonal antibody. The monoclonal antibody may be 5c8 (ATCC Accession No. HB 10916).

10 The anti-CD40L compound may be formulated in a therapeutic composition which includes a therapeutically-effective amount of the anti-CD40L compound and a pharmaceutically acceptable carrier. The therapeutic composition may also include a second therapeutically effective compound.

Brief Description of the Drawings

15 Fig. 1 is a chart of the changes with time in several measured characteristics of blood and urine from control and treated (SWR X NZB) F₁ mice in Experiment II. The anti-CD40L mAb MR1, at 500 ug/animal i.p., was administered once when the mice were 4 months old, again at 7 months of age, again at 9 months, and then at monthly intervals. Each of the upper five rows of the chart, marked AR-BN, contains data from a single control animal, and each of
20 the lower six rows, marked CL-CR, contains data from a single treated animal. This study began when the animals were 4 months of age, in February 1996. The vertical double lines separate 4 groups of data, each data group providing the measurements for urine and blood samples collected on the date listed above the data. Proteinuria (PU) levels are indicated from trace to level 4. Level 1 correlates with urine albumin of 30 mg/dl albumin, level 2 with
25 100 mg/dl, level 3 with 300 mg/dl, and level 4 with over 2000 mg/dl. Levels of anti-MR1 antibodies (provided in column labeled "anti-MR1"), anti-ssDNA antibodies and anti-dsDNA antibodies are given in µg/ml blood. Where appropriate, values are given as mean and standard deviation of several samples, in the form mean(S.D.). A dash indicates that a sample was not collected, typically because the animal had died. ND refers to "not done."

-4-

Fig. 2 is a chart of proteinuria measurements of the Experiment II animals over time. The first column provides the animal numbers as in Fig. 1. The columns are headed with the dates of sample collection. NC means "not collected."

5 Fig. 3 is a chart of blood and urine characteristics with time in Experiment V control and untreated mice, which started treatment at 4.5 months of age. MR1 was administered to treated animals once at 500 ug/animal i.p. when the mice were 4.5 months old, and then as monthly injections of 500 ug, i.p. Each of the upper seven rows of the chart, marked AR-BLR, contains data from a single control animal, and each of the lower seven rows, marked
10 CR -CLR, contains data from a single treated animal. This study began when the animals were 4.5 months of age, in May 1996. Other descriptions of the figure are the same as those of Fig. 1.

Fig. 4 is a chart of proteinuria measurements of the Experiment V animals over time. Animal
15 numbers are as described for Fig. 3. Other descriptions of the figure are the same as those of Fig. 2.

Fig. 5 is a chart of chart of blood and urine characteristics with time in Experiment VII control and untreated mice, which started treatment at 5.5 months of age. MR1 was administered to
20 treated animals once weekly at 500 ug/animal i.p. for six weeks, followed by monthly injections of 500 ug, i.p. Each of the upper three rows of the chart, marked AN-BL, contains data from a single control animal (as noted in Fig. 6, some control animals had died before the data for Fig. 5 was collected), and each of the lower seven rows, marked CR-DN, contains data from a single treated animal. This study began when the animals were 5.5 months of
25 age, in June 1996. Other descriptions of the figure are the same as those of Fig. 1.

Fig. 6 is a chart of proteinuria measurements of the Experiment VII animals over time. Each of the upper seven rows of the chart, marked AR-BN, contains data from a single control animal, and each of the lower seven rows, marked CR-DN, contains data from a single
30 treated animal. Other descriptions of the figure are the same as those of Fig. 2.

-5-

Fig. 7 is a chart of blood and urine characteristics with time in Experiment X control and untreated mice, which started treatment at 5.5 months of age. MR1 was administered to treated animals once weekly at 500 ug/animal i.p. for four weeks, followed by monthly injections of 200 ug, i.p. Each of the upper eight rows of the chart, marked AR-BLR, contains data from a single control animal, and each of the lower eight rows, marked CR-DLR, contains data from a single treated animal. This study began when the animals were 5.5 months of age, in October 1996. Other descriptions of the figure are the same as those of Fig. 1.

10

Fig. 8 is a chart of proteinuria measurements of the Experiment X animals over time. The first column provides the animal numbers as in Fig. 7. Other descriptions of the figure are the same as those of Fig. 2.

Fig. 9 is a chart of blood and urine characteristics with time in Experiment VI control and untreated mice, which started treatment at 7 months of age. MR1 was administered to 4 treated animals once weekly at 500 ug/animal i.p. for six weeks, followed by monthly injections of 500 ug, i.p. Each of the lower four rows, marked DN-EN, contains data from a single treated animal. At the time of first data collection for this chart, all control animals had died, as noted Fig. 10. This study began when the animals were 7 months of age, in June 1996. Other descriptions of the figure are the same as those of Fig. 1.

20

Fig. 10 is a chart of proteinuria measurements of the Experiment VI animals over time. Each of the upper four rows of the chart, marked AR-CN, contains data from a single control animal, and each of the lower four rows, marked DN-EN, contains data from a single treated animal. Other descriptions of the figure are the same as those of Fig. 2.

25

Detailed Description of the Invention

The method of the invention involves treating, preventing, reversing or stabilizing a patient with an antibody-related disease, by treating the patient with an anti-CD40L

30

-6-

compound at intervals of more than two weeks. The compound blocks the interaction of CD40L on T cells with CD40 on B cells, which is thought to inhibit the production of pathologic antibodies responsible for many of the pathologic effects of various autoimmune diseases and chronic immune disorders.

5

Compounds

Therapeutic compounds useful for the methods of the invention include any compound that blocks the interaction of CD40 on B cells with CD40L expressed on the surface of activated T cells. Anti-CD40L compounds specifically contemplated include polyclonal
10 antibodies and monoclonal antibodies (mAbs), as well as antibody derivatives such as chimeric molecules, humanized molecules, molecules with reduced effector functions, bispecific molecules, and conjugates of antibodies. In a preferred embodiment, the antibody is 5c8, as described in U.S. Patent 5,474,771, the specification of which is hereby incorporated by reference. Other known antibodies against 5c8 antigen include antibodies ImxM90,
15 ImxM91 and ImxM92 (obtained from Immunex), an anti-CD40L mAb commercially available from Ancell (clone 24-31, catalog # 353-020, Bayport, MN), and an anti-CD40L mAb commercially available from Genzyme (Cambridge, MA, catalog # 80-3703-01). Also commercially available is an anti-CD40L mAb from PharMingen (San Diego, catalog #33580D). Numerous additional anti-CD40L antibodies have been produced and
20 characterized (see, e.g., WO 96/23071 of Bristol-Myers Squibb, the specification of which is hereby incorporated by reference).

The invention also includes anti-CD40L molecules of other types, such as complete Fab fragments, $F(ab')_2$ compounds, V_H regions, F_V regions, single chain antibodies (see, e.g., WO 96/23071), polypeptides, fusion constructs of polypeptides, fusions of CD40 (such as
25 CD40Ig, as in Hollenbaugh et al., J. Immunol. Meth. 188:1-7, 1995, which is hereby incorporated by reference), and small molecule compounds such as small semi-peptidic compounds or non-peptide compounds, all capable of blocking the CD40-CD40L interaction. Procedures for designing, screening and optimizing small molecules are provided in the patent application PCT/US96/10664, filed June 21, 1996, the specification of which is hereby
30 incorporated by reference.

-7-

Various forms of antibodies may also be produced using standard recombinant DNA techniques (Winter and Milstein, Nature 349: 293-99, 1991). For example, "chimeric" antibodies may be constructed, in which the antigen binding domain from an animal antibody is linked to a human constant domain (an antibody derived initially from a nonhuman mammal in which recombinant DNA technology has been used to replace all or part of the hinge and constant regions of the heavy chain and/or the constant region of the light chain, with corresponding regions from a human immunoglobulin light chain or heavy chain) (see, e.g., Cabilly et al., United States patent 4,816,567; Morrison et al., Proc. Natl. Acad. Sci. 81: 6851-55, 1984). Chimeric antibodies reduce the immunogenic responses elicited by animal antibodies when used in human clinical treatments.

In addition, recombinant "humanized" antibodies may be synthesized. Humanized antibodies are antibodies initially derived from a nonhuman mammal in which recombinant DNA technology has been used to substitute some or all of the amino acids not required for antigen binding with amino acids from corresponding regions of a human immunoglobulin light or heavy chain (chimeras comprising mostly human IgG sequences into which the regions responsible for specific antigen-binding have been inserted)(see, e.g., PCT patent application WO 94/04679). Animals are immunized with the desired antigen, the corresponding antibodies are isolated and the portion of the variable region sequences responsible for specific antigen binding are removed. The animal-derived antigen binding regions are then cloned into the appropriate position of the human antibody genes in which the antigen binding regions have been deleted. Humanized antibodies minimize the use of heterologous (inter-species) sequences in human antibodies and are less likely to elicit immune responses in the treated subject.

Also useful in the methods and compositions of this invention are primate or primatized antibodies.

Antibody fragments and univalent antibodies may also be used in the methods and compositions of this invention. Univalent antibodies comprise a heavy chain/light chain dimer bound to the Fc (or stem) region of a second heavy chain. "Fab region" refers to those portions of the chains which are roughly equivalent, or analogous, to the sequences which comprise the Y branch portions of the heavy chain and to the light chain in its entirety, and

-8-

which collectively (in aggregates) have been shown to exhibit antibody activity. A Fab protein includes aggregates of one heavy and one light chain (commonly known as Fab'), as well as tetramers which correspond to the two branch segments of the antibody Y, (commonly known as F(ab)₂), whether any of the above are covalently or non-covalently aggregated, so long as the aggregation is capable of selectively reacting with a particular antigen or antigen family.

In addition, standard recombinant DNA techniques can be used to alter the binding affinities of recombinant antibodies with their antigens by altering amino acid residues in the vicinity of the antigen binding sites. The antigen binding affinity of a humanized antibody may be increased by mutagenesis based on molecular modeling (Queen et al., Proc. Natl. Acad. Sci. 86:10029-33, 1989; PCT patent application WO 94/04679). It may be desirable to increase or to decrease the affinity of the antibodies for CD40L, depending on the targeted tissue type or the particular treatment schedule envisioned. This may be done utilizing phage display technology (see, e.g., Winter et al., Ann. Rev. Immunol. 12:433-455, 1994; and Schier et al., J. Mol. Biol. 255:28-43, 1996, which are hereby incorporated by reference). For example, it may be advantageous to treat a patient with constant levels of antibodies with reduced affinity for CD40L for semi-prophylactic treatments. Likewise, antibodies with increased affinity for CD40L may be advantageous for short-term treatments.

20 Subjects

The term "patient" is taken to mean any mammalian patient to which anti-CD40L compounds may be administered. Patients specifically intended for treatment with the method of the invention include humans, as well as nonhuman primates, sheep, horses, cattle, goats, pigs, dogs, cats, rabbits, guinea pigs, hamsters, gerbils, rats and mice, as well as the organs, tumors, and cells derived or originating from these hosts.

The subjects for which the methods of the invention are intended have disease related to antibody production.

Routes of Administration

-9-

The compounds of the invention may be administered in any manner which is medically acceptable. This may include injections, by parenteral routes such as intravenous, intravascular, intraarterial, subcutaneous, intramuscular, intratumor, intraperitoneal, intraventricular, intraepidural, or others as well as oral, nasal, ophthalmic, rectal, or topical.

5 Sustained release administration is also specifically included in the invention, by such means as depot injections. Some forms of anti-CD40L compounds may be suitable for oral administration, and could be formulated as suspensions or pills.

Dosages and Frequency of Treatment

10 The amount of and frequency of dosing for any particular compound to be administered to a patient for a given immune complex disease is a judgment made by the patient's physician, based on a number of factors. The general dosage is established by preclinical and clinical trials, which involve extensive experiments to determine the beneficial and deleterious effects on the patient of different dosages of the compound. Even after such

15 recommendations are made, the physician will often vary these dosages for different patients based on a variety of considerations, such as a patient's age, medical status, weight, sex, and concurrent treatment with other pharmaceuticals. Determining the optimal dosage for each anti-CD40L compound used to treat lupus nephritis is a routine matter for those of skill in the pharmaceutical and medical arts.

20 Various regimens may be used for treatment of lupus or other immune complex diseases according to this invention. Generally, the frequency of dosing would be determined by the attending physician, and might include periods of greater dosing frequency, such as at daily or weekly intervals, alternating with periods of less frequent dosing, such as at monthly or longer intervals.

25 To exemplify dosing considerations for an anti-CD40L compound, the following examples of administration strategies are given for an anti-CD40L mAb. The dosing amounts could easily be adjusted for other types of anti-CD40L compounds. In general, single dosages of between about 0.05 and about 50 mg/kg patient body weight are contemplated, with dosages most frequently in the 1-20 mg/kg range. For acute treatment, an effective dose

30 of antibodies ranges from about 1 mg/kg body weight to about 20 mg/kg body weight,

-10-

administered daily for a period of about 1 to 5 days, preferably by bolus intravenous administration. The same dosage and dosing schedule may be used in the load phase of a load-maintenance regimen, with the maintenance phase involving intravenous or intramuscular administration of antibodies in a range of about 0.1 mg/kg body weight to about 20 mg/kg body weight, for a treatment period of anywhere from weekly to 3 month intervals. Chronic treatment may also be carried out by a maintenance regimen, in which antibodies are administered by intravenous or intramuscular route, in a range of about 0.1 mg/kg body weight to about 20 mg/kg body weight, with interdose intervals being anywhere between about 1 week and about to 3 months. In addition, chronic treatment may be effected by an intermittent bolus intravenous regimen, in which between about 1.0 mg/kg body weight and about 100 mg/kg body weight of antibodies are administered, with the interval between successive treatments being from 1 to 6 months. For all except the intermittent bolus regimen, administration may also be by oral, pulmonary, nasal or subcutaneous routes.

Generally, therapy is commenced with low doses of antibodies. For example, an initial dose of antibodies is administered to the patient by, for example, injection or infusion. That initial dose should contain between about 1.0 mg and 30 mg of antibodies per day for a 70 kg patient. For repeated administrations over several days, dosages may be administered on successive days, every two to six days, once a week, every two to four weeks or once a month, until a desired suppression of disease symptoms is observed. However, other dosage regimens are also useful. When the symptoms have been alleviated to the desired level, treatment may cease. Patients may, however, require intermittent treatment on a long term basis upon recurrence of disease symptoms.

According to an alternate embodiment of this invention for treatment of lupus or other antibody-related diseases, the effectiveness of the antibodies may be increased by administration serially or in combination with conventional anti-lupus therapeutic agents or drugs such as, for example, salicylates, corticosteroids or immunosuppressants. Alternatively, the antibodies may be conjugated to a conventional agent. This advantageously permits the administration of the conventional agent in an amount less than the conventional dosage, for example, less than about 50% of the conventional dosage, when the agent is administered as

-11-

monotherapy. Accordingly, the occurrence of many side effects associated with that agent might be avoided.

Combination therapies according to this invention for treatment of lupus include the use of anti-CD40L antibodies together with agents targeted at B cells, such as anti-CD19, anti-
5 CD28 or anti-CD20 antibody (unconjugated or radiolabeled), IL-14 antagonists, LJP394 (LaJolla Pharmaceuticals receptor blocker), IR-1116 (Takeda small molecule) and anti-Ig idiotype monoclonal antibodies. Alternatively, the combinations may include T cell/B cell targeted agents, such as CTLA4Ig, IL-2 antagonists, IL-4 antagonists, IL-6 antagonists, receptor antagonists, anti-B7 monoclonal antibodies, TNF, LFA1/ICAM antagonists,
10 VLA4/VCAM antagonists, brequinar and IL-2 toxin conjugates (e.g., DAB), prednisone, cyclophosphamide, and other immunosuppressants. Combinations may also include T cell targeted agents, such as CD4 antagonists, CD2 antagonists and IL-12.

Combination therapies for treatment of a patient with a non-lupus immune complex disease might involve administration of an anti-CD40L compound as well as an agent which
15 would typically be administered for the particular immune complex disease in question.

Once improvement of the patient's condition has occurred, a maintenance dose of anti-CD40L antibodies, alone or in combination with a conventional anti-lupus agent is administered, if necessary. Subsequently, the dosage or the frequency of administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved
20 condition is retained. When the symptoms have been alleviated to the desired level, treatment might cease. In other instances, as determined by a patient's physician, occasional treatment might be administered, for example at intervals of four weeks or more. Patients may, however, require intermittent treatment on a long-term basis upon any recurrence of disease symptoms.

25

Formulation

An anti-CD40L compound used in the methods of the invention is administered in a pharmaceutically-effective amount, which is an amount which produces a medically beneficial effect on a patient with an antibody-related disease, an immune-associated disorder, or a
30 patient with a transplant or a transgene for which suppression of rejection is desirable..

-12-

Medically beneficial effects would include preventing deterioration or causing improvement in the patient's medical condition. As an example, an organ that is often damaged by pathologic antibodies is the kidney in SLE patients. In these patients, treated with the methods of the invention, renal function and health may be monitored with one or more
5 laboratory tests which measure the concentrations of relevant substances in blood or urine, other urine characteristics, or the rate of clearance of various substances from the blood into the urine. The parameters measured by these tests, either individually or in combination, can be used by a physician to assess renal function or damage. Examples of such parameters include the blood concentration of urea, creatinine or protein; the urine concentration of
10 protein or of various blood cells such as erythrocytes or leucocytes; urine specific gravity; amount of urine; the clearance rates of inulin, creatinine, urea or p-aminohippuric acid; and the presence of hypertension or edema. Medically beneficial effects would also include the diminution of autoantibodies, such as anti-dsDNA antibodies in the serum of lupus patients.

An anti-CD40L compound of the invention is administered to a patient in a
15 pharmaceutically acceptable composition, which may include a pharmaceutically-acceptable carrier. Such a carrier is relatively non-toxic and innocuous to a patient at concentrations consistent with effective activity of the anti-CD40L compound or other active ingredients, so that any side effects ascribable to the carrier do not vitiate the beneficial effects of the active ingredients of the composition. The composition may include other compatible substances;
20 compatible, as used herein, means that the components of the pharmaceutical composition are capable of being commingled with the anti-CD40L compound, and with each other, in a manner such that there is no interaction which would substantially reduce the therapeutic efficacy of the pharmaceutical. Nasal spray formulations comprise purified aqueous solutions of the active compound with preservative agents and isotonic agents. Such formulations are
25 preferably adjusted to a pH and isotonic state compatible with the nasal mucous membranes. Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets, tablets, pills or lozenges, each containing a predetermined amount of the potentiating anti-CD40L compound as a powder or granules; as liposomes; or as a suspension in an aqueous liquor or non-aqueous liquid such as a syrup, an
30 elixir, an emulsion or a draught.

Use of Anti-CD40L Compounds Administered at Wide Intervals to Treat Lupus Nephritis in Nonhuman Subjects

We chose to demonstrate the efficacy of administering anti-CD40L compounds in an animal model of lupus nephritis. Systemic lupus erythematosus (SLE) is a life threatening autoimmune disease, characterized by the production of autoantibodies against various tissues, and often against DNA. SLE affects approximately 140,000 people in the United States and 105,000 in western Europe, predominantly women of childbearing age. In most patients, lupus-associated immunoglobulins and immune complexes are deposited in the renal glomeruli, causing a decline in renal function. If widely spaced doses of anti-CD40L compounds are efficacious in selectively suppressing antibody production, such a dosing regime would exert beneficial effects on nephritis. This could be evidenced in treated animals by slower progression of nephritis, reduced severity of nephritis, enhanced survival, or even by improvement of renal function in some animals.

We tested the effects of the hamster anti-muCD40L mAb MR1 on the course of nephritis in the female (SWR X NZB) F₁ mouse, in several studies as described below. Control animals were injected either with Syrian hamster polyclonal Ig or with Ha4/8, an Armenian hamster mAb directed against KLH. Proteinuria levels are indicated from trace to level 4. Level 1 correlates with urine albumin of 30 mg/dl albumin, level 2 with 100 mg/dl, level 3 with 300 mg/dl, and level 4 with over 2000 mg/dl. A level of 2 was considered to indicate moderate nephritis, with 2.5 and greater indicating severe nephritis.

If untreated, or if treated with the nonspecific hamster immunoglobulins administered to control animals, the mice normally die by 12 months of age. While the onset of proteinuria in untreated animals is variable, most have mild to moderate proteinuria by 3 months of age; the proteinuria tends to increase with age. By about 5 months of age, all control animals typically have detectable anti-dsDNA antibodies, and most have detectable anti-ssDNA antibodies; this contrasts with the complete lack of detectable levels of these antibodies in normal mice, such as the female SWR parents of the (SWR X NZB) F₁ mice.

Experiment II: Treatment begun at 4 months (Figs. 1 and 2)

-14-

MR1 treatment was initiated when the mice were 4 months of age. MR1 was administered to treated animals once at 500 ug/animal i.p. when the mice were 4 months old, once at 7 months of age, and once at 9 months followed by once-monthly injections. After 4 months of treatment, 4 of the 5 control animals had died, but four of the six treated animals were yet alive. Three of these four previously surviving treated mice died, one each at 12, 13 and 13.5 months. One still survives, and is now 15 months old, an extraordinary longevity for mice of this cross. Of great interest, the surviving animal (mouse II:DN on Figure 2) had moderate nephritis (2+ proteinuria) from ages 8 to 13 months, which has decreased to only trace levels of proteinuria for the last two months. This is the first demonstration of a functional reversal of nephritis in a mouse of this strain.

Experiment V: Treatment begun at 4.5 months (Figs. 3 and 4)

MR1 treatment was initiated when the mice were 4.5 months of age. MR1 was administered to treated animals once at 500 ug/animal i.p. when the mice were 4.5 months old, and then as monthly injections of 500 ug, i.p. After 4.5 months, 6 of the 7 control animals had died, but six of the seven treated animals survived. After 8 months of treatment, all controls were dead, but only three of the seven treated mice had died. As shown in Fig. 4, four of the seven MR1-treated animals had their nephritis reversed as shown by sustained lowered proteinuria levels. These four animals are still alive at age 12.5 months.

Experiment VII: Treatment begun at 5.5 months (Figs. 5 and 6)

MR1 treatment was initiated when the mice were 5.5 months of age. MR1 at 500 µg/animal i.p. was administered to treated animals once weekly for six weeks, followed by monthly injections. After 5 months of treatment, at age 10.5 months, 6 of the 7 control animals had died; all of the 7 treated animals are still alive at age 12 months. The following values were measured in the animals which still survived at 8.5 months, after 3.5 months of treatment:

	<u>anti-SS-DNA</u>	<u>anti-DS DNA</u>	<u>PU</u>
control	2.4	0	4

		-15-	
	8.8	6.3	4
	6.3	10.1	4
Mean (Std. Dev.)	5.8 (2.6)	5.4 (4.1)	4 (0)
5 MR1	2.7	0	1
	2.0	0	1.5
	2.0	1.5	3
	0	0	2
	2.7	0	1
10	0	0	2
	3.5	0	1.5
Mean (Std. Dev.)	1.8 (1.2)	0.2 (0.5)	1.7 ()

Experiment X: Less intensive treatment, begun at 5.5 months (Figs. 7 and 8)

15 MR1 treatment was initiated when the mice were 5.5 months of age. MR1 was administered to treated animals once weekly at 500 ug/animal i.p. for four weeks, followed by monthly injections of 200 µg, i.p. Of the 16 mice in the study (8 each in control and treated groups), now 8.5 months of age, only one mouse has died, a control animal at age 7.5 months. As shown in Fig. 8, seven of the eight control animals had proteinuria which steadily

20 increased to high levels, averaging +3.4 for the 7 surviving control mice. All but one of the eight MR1- treated mice have maintained low proteinuria, which currently averages +2 for the 8 treated mice. As shown in Fig. 7, six of the treated animals, but only one of the controls, have no detectable anti-dsDNA antibodies.

25 Experiment VI: Treatment begun at 7 months (Figs. 9 and 10)

MR1 treatment was initiated when the mice were seven months of age. MR1 was administered to 4 treated animals once weekly at 500 ug/animal i.p. for six weeks, followed by monthly injections of 500 ug, i.p. By age 10 months, all 4 control animals had died. While 2 of the treated mice died at age 11 months, and a third at 13 months, one of the four treated

30 animals remains alive currently at 14 months of age, after 7 months of treatment. The

-16-

surviving treated animal (number VI:ER) currently has level 1 proteinuria, and detectable anti-dsDNA and anti-ssDNA antibodies.

These experiments show that treatment of (SWR X NZB) F₁ mice with anti-CD40L mAb, administered for at least a period of time at intervals of over 3 weeks, markedly and consistently prolongs survival as compared to control animals, and slows development of nephritis as indicated by proteinuria levels. In some animals, the treatment actually reverses nephritis, as shown by a reduction in proteinuria levels. Of 32 treated animals, 11 had urine protein levels which decreased with anti-CD40L mAb therapy; none of the control animals had similar reductions. Of 24 treated animals in which serum blood urea nitrogen (BUN) was measured, 3 had decreases in BUN levels after treatment, which was not observed in any control animal. In addition, MR1 treatment often results in a reduced serum concentration of anti-DS and anti-SS DNA autoantibodies, which are normally produced in untreated animals of this type.

The disease-reducing or -preventing results of these experiments demonstrate that anti-CD40L compounds may successfully be used to treat antibody-associated conditions when administered at intervals of 3 or more weeks. This is a surprising and unanticipated finding, which confers significant advantages over previously contemplated dosing regimens. Particularly for patients being treated for a chronic disease, reduced frequency of treatments results in lowered cost, inconvenience, and discomfort, particularly for injectable or intravenous treatments. In addition, any side effects of treatment would be expected to be reduced with fewer and more widely spaced dosings.

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be obvious to one skilled in the art that certain changes and modifications may be practiced within the scope of the invention, as limited only by the scope of the appended claims.

-17-

Claims

1. A method of treating a patient with an antibody-related disease, comprising administering a therapeutically effective amount of an anti-CD40L compound to the patient on a first day and again on a second day, with at least about 3 weeks between the first day and the second day.
- 5 2. The method of claim 1, further comprising administering a therapeutically effective amount of an anti-CD40L compound to the patient on a third day, with an interval of at least about 3 weeks between the second day and the third day.
- 10 3. The method of claim 1, wherein the interval between the first day and the second day is at least about 4 weeks, at least about 6 weeks, or at least about 8 weeks.
4. A method of treating a patient with an antibody-related disease, comprising administering a therapeutically effective amount of an anti-CD40L compound to the patient for a first
15 therapeutic period at intervals of less than about 3 weeks, then administering a therapeutically effective amount of an anti-CD40L compound to the patient for a second therapeutic period at intervals of at least about 3 weeks.
5. The method of claim 4, wherein the anti-CD40L compound is administered for the second
20 therapeutic period at intervals of at least about 4 weeks.
6. A method of treating a patient with a chronic autoimmune disease, comprising administering a therapeutically effective amount of an anti-CD40L compound to the patient on a first day and again on a second day, with at least about 3 weeks between the first day and
25 the second day.
7. The method of claim 6, further comprising administering a therapeutically effective amount of an anti-CD40L compound to the patient on a third day, with at least about 3 weeks between the second day and the third day.

-18-

8. The method of claim 6, wherein there is at least about 4 weeks between the first day and the second day.

9. A method of treating a patient with a chronic immune system disorder, comprising
5 administering a therapeutically effective amount of an anti-CD40L compound to the patient for a first therapeutic period at intervals of less than about 3 weeks, then administering a therapeutically effective amount of an anti-CD40L compound to the patient for a second therapeutic period at intervals of at least about 3 weeks.

10 10. The method of claim 9, wherein the anti-CD40L compound is administered for the second therapeutic period at intervals of at least about 4 weeks.

11. The method of claim 9, wherein the chronic immune disorder is systemic lupus erythematosus, an allergic disorder, myasthenia gravis, autoimmune hemolytic anemia,
15 idiopathic thrombocytopenic purpura, or anti-phospholipid syndrome.

12. The method of claim 9, wherein the chronic immune disorder is psoriasis, arthritis or multiple sclerosis.

20 13. The method of claim 9, wherein the anti-CD40L compound is an anti-CD40L antibody.

14. The method of claim 13, wherein the antibody is a monoclonal antibody.

15. The method of claim 14, wherein the monoclonal antibody is 5c8.

25

16. The method of claim 9, wherein the anti-CD40L compound is formulated in a therapeutic composition comprising a therapeutically-effective amount of the anti-CD40L compound and a pharmaceutically acceptable carrier.

-19-

17. The method of claim 16, wherein the therapeutic composition further comprises a second therapeutically effective compound.

18. A method of inhibiting rejection of transplanted tissue within a patient, comprising
5 administering a therapeutically effective amount of an anti-CD40L compound to the patient on a first day and again on a second day, with at least about 3 weeks between the first day and the second day.

19. The method of claim 18, further comprising administering a therapeutically effective
10 amount of an anti-CD40L compound to the patient on a third day, with at least about 3 weeks between the second day and the third day.

20. The method of claim 18, wherein there is at least about 4 weeks between the first day and the second day.

15

21. The method of claim 18, wherein the transplanted tissue is a kidney, liver, or heart.

22. The method of claim 18, wherein the transplanted tissue is an allograft or a xenograft.

20 23. A method of inhibiting rejection of transplanted tissue within a patient, comprising administering a therapeutically effective amount of an anti-CD40L compound to the patient for a first therapeutic period at intervals of less than about 3 weeks, then administering a therapeutically effective amount of an anti-CD40L compound to the patient for a second therapeutic period at intervals of at least about 3 weeks.

25

24. A method of inhibiting immune reaction to the gene product of a transgene within a patient, comprising administering a therapeutically effective amount of an anti-CD40L compound to the patient on a first day and again on a second day, with at least about 3 weeks between the first day and the second day.

Figure .1

[illegible]

[illegible]

Figure 3

		PRE-5-2-96			10-4-96	8/18 5 [n]			11-15-96	10/15	
										6[n]	
V	PU	Anti-SSDNA ug/ml	Anti-DSDNA ug/ml	PU	MRI ug/ml	Anti-MRI ug/ml	Anti-SSDNA ug/ml	Anti-DSDNA ug/ml	PU	MRI ug/ml	Anti-M ug/ml
AR	1r	13.4(1.3)	4.3(0.5)	-	-	-	-	-	-	-	-
AL	1r	0	0	-	-	-	-	-	-	-	-
AN	1r	5.4(0.8)	1.3(0.3)	-	-	-	-	-	-	-	-
BR	2	2.8(0.1)	0	-	-	-	-	-	-	-	-
BL	2	0.8(0.09)	0	-	-	-	-	-	-	-	-
BN	2	0	0	4+	ND	ND	13.2 (1.1)	3.3 (0.3)	4+	ND	ND
BR	2	0	0	-	-	-	-	-	-	-	-
CR	2	1.2(0.1)	2.3(0.3)	4	30 (4.6)	ND	0	0	-	-	-
CL	1	0.8(0.1)	0	1	0	926(51)	2.6 (0.3)	0	1	0	0.2(0.00)
CN	1	0	0	1	68 (3.5)	ND	0	0	1	39(6.4)	0
DR	1	0	0	2	143 (27)	ND	0	0	1	77.5(8.4)	0
DL	2	2.8(0.2)	0	1.5	36.6 (8.7)	ND	0	0	1.5	30.4(6.8)	0.5(0.00)
DN	1r	1.9(0.1)	0	-	-	-	-	-	-	-	-
DR	1	0	0	-	-	-	-	-	-	-	-

Figure 4

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100	101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	116	117	118	119	120	121	122	123	124	125	126	127	128	129	130	131	132	133	134	135	136	137	138	139	140	141	142	143	144	145	146	147	148	149	150	151	152	153	154	155	156	157	158	159	160	161	162	163	164	165	166	167	168	169	170	171	172	173	174	175	176	177	178	179	180	181	182	183	184	185	186	187	188	189	190	191	192	193	194	195	196	197	198	199	200	201	202	203	204	205	206	207	208	209	210	211	212	213	214	215	216	217	218	219	220	221	222	223	224	225	226	227	228	229	230	231	232	233	234	235	236	237	238	239	240	241	242	243	244	245	246	247	248	249	250	251	252	253	254	255	256	257	258	259	260	261	262	263	264	265	266	267	268	269	270	271	272	273	274	275	276	277	278	279	280	281	282	283	284	285	286	287	288	289	290	291	292	293	294	295	296	297	298	299	300	301	302	303	304	305	306	307	308	309	310	311	312	313	314	315	316	317	318	319	320	321	322	323	324	325	326	327	328	329	330	331	332	333	334	335	336	337	338	339	340	341	342	343	344	345	346	347	348	349	350	351	352	353	354	355	356	357	358	359	360	361	362	363	364	365	366	367	368	369	370	371	372	373	374	375	376	377	378	379	380	381	382	383	384	385	386	387	388	389	390	391	392	393	394	395	396	397	398	399	400	401	402	403	404	405	406	407	408	409	410	411	412	413	414	415	416	417	418	419	420	421	422	423	424	425	426	427	428	429	430	431	432	433	434	435	436	437	438	439	440	441	442	443	444	445	446	447	448	449	450	451	452	453	454	455	456	457	458	459	460	461	462	463	464	465	466	467	468	469	470	471	472	473	474	475	476	477	478	479	480	481	482	483	484	485	486	487	488	489	490	491	492	493	494	495	496	497	498	499	500	501	502	503	504	505	506	507	508	509	510	511	512	513	514	515	516	517	518	519	520	521	522	523	524	525	526	527	528	529	530	531	532	533	534	535	536	537	538	539	540	541	542	543	544	545	546	547	548	549	550	551	552	553	554	555	556	557	558	559	560	561	562	563	564	565	566	567	568	569	570	571	572	573	574	575	576	577	578	579	580	581	582	583	584	585	586	587	588	589	590	591	592	593	594	595	596	597	598	599	600	601	602	603	604	605	606	607	608	609	610	611	612	613	614	615	616	617	618	619	620	621	622	623	624	625	626	627	628	629	630	631	632	633	634	635	636	637	638	639	640	641	642	643	644	645	646	647	648	649	650	651	652	653	654	655	656	657	658	659	660	661	662	663	664	665	666	667	668	669	670	671	672	673	674	675	676	677	678	679	680	681	682	683	684	685	686	687	688	689	690	691	692	693	694	695	696	697	698	699	700	701	702	703	704	705	706	707	708	709	710	711	712	713	714	715	716	717	718	719	720	721	722	723	724	725	726	727	728	729	730	731	732	733	734	735	736	737	738	739	740	741	742	743	744	745	746	747	748	749	750	751	752	753	754	755	756	757	758	759	760	761	762	763	764	765	766	767	768	769	770	771	772	773	774	775	776	777	778	779	780	781	782	783	784	785	786	787	788	789	790	791	792	793	794	795	796	797	798	799	800	801	802	803	804	805	806	807	808	809	810	811	812	813	814	815	816	817	818	819	820	821	822	823	824	825	826	827	828	829	830	831	832	833	834	835	836	837	838	839	840	841	842	843	844	845	846	847	848	849	850	851	852	853	854	855	856	857	858	859	860	861	862	863	864	865	866	867	868	869	870	871	872	873	874	875	876	877	878	879	880	881	882	883	884	885	886	887	888	889	890	891	892	893	894	895	896	897	898	899	900	901	902	903	904	905	906	907	908	909	910	911	912	913	914	915	916	917	918	919	920	921	922	923	924	925	926	927	928	929	930	931	932	933	934	935	936	937	938	939	940	941	942	943	944	945	946	947	948	949	950	951	952	953	954	955	956	957	958	959	960	961	962	963	964	965	966	967	968	969	970	971	972	973	974	975	976	977	978	979	980	981	982	983	984	985	986	987	988	989	990	991	992	993	994	995	996	997	998	999	1000	1001	1002	1003	1004	1005	1006	1007	1008	1009	1010	1011	1012	1013	1014	1015	1016	1017	1018	1019	1020	1021	1022	1023	1024	1025	1026	1027	1028	1029	1030	1031	1032	1033	1034	1035	1036	1037	1038	1039	1040	1041	1042	1043	1044	1045	1046	1047	1048	1049	1050	1051	1052	1053	1054	1055	1056	1057	1058	1059	1060	1061	1062	1063	1064	1065	1066	1067	1068	1069	1070	1071	1072	1073	1074	1075	1076	1077	1078	1079	1080	1081	1082	1083	1084	1085	1086	1087	1088	1089	1090	1091	1092	1093	1094	1095	1096	1097	1098	1099	1100	1101	1102	1103	1104	1105	1106	1107	1108	1109	1110	1111	1112	1113	1114	1115	1116	1117	1118	1119	1120	1121	1122	1123	1124	1125	1126	1127	1128	1129	1130	1131	1132	1133	1134	1135	1136	1137	1138	1139	1140	1141	1142	1143	1144	1145	1146	1147	1148	1149	1150	1151	1152	1153	1154	1155	1156	1157	1158	1159	1160	1161	1162	1163	1164	1165	1166	1167	1168	1169	1170	1171	1172	1173	1174	1175	1176	1177	1178	1179	1180	1181	1182	1183	1184	1185	1186	1187	1188	1189	1190	1191	1192	1193	1194	1195	1196	1197	1198	1199	1200	1201	1202	1203	1204	1205	1206	1207	1208	1209	1210	1211	1212	1213	1214	1215	1216	1217	1218	1219	1220	1221	1222	1223	1224	1225	1226	1227	1228	1229	1230	1231	1232	1233	1234	1235	1236	1237	1238	1239	1240	1241	1242	1243	1244	1245	1246	1247	1248	1249	1250	1251	1252	1253	1254	1255	1256	1257	1258	1259	1260	1261	1262	1263	1264	1265	1266	1267	1268	1269	1270	1271	1272	1273	1274	1275	1276	1277	1278	1279	1280	1281	1282	1283	1284	1285	1286	1287	1288	1289	1290	1291	1292	1293	1294	1295	1296	1297	1298	1299	1300	1301	1302	1303	1304	1305	1306	1307	1308	1309	1310	1311	1312	1313	1314	1315	1316	1317	1318	1319	1320	1321	1322	1323	1324	1325	1326	1327	1328	1329	1330	1331	1332	1333	1334	1335	1336	1337	1338	1339	1340	1341	1342	1343	1344	1345	1346	1347	1348	1349	1350	1351	1352	1353	1354	1355	1356	1357	1358	1359	1360	1361	1362	1363	1364	1365	1366	1367	1368	1369	1370	1371	1372	1373	1374	1375	1376	1377	1378	1379	1380	1381	1382	1383	1384	1385	1386	1387	1388	1389	1390	1391	1392	1393	1394	1395	1396	1397	1398	1399	1400	1401	1402	1403	1404	1405	1406	1407	1408	1409	1410	1411	1412	1413	1414	1415	1416	1417	1418	1419	1420	1421	1422	1423	1424	1425	1426	1427	1428	1429	1430	1431	1432	1433	1434	1435	1436	1437	1438	1439	1440	1441	1442	1443	1444	1445	1446	1447	1448	1449	1450	1451	1452	1453	1454	1455	1456	1457	1458	1459	1460	1461	1462	1463	1464	1465	1466	1467	1468	1469	1470	1471	1472	1473	1474	1475	1476	1477	1478	1479	1480	1
---	---	---	---	---	---	---	---	---	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	---

PU	0-30-86 HRI ug/ml	03-7-84 Anti-MRI ug/ml	Anti-ssDNA ug/ml	Anti-dsDNA ug/ml	Total (g) mg/ml	PU	11-1-86 HRI ug/ml	Anti-MRI ug/ml	Anti-ssDNA ug/ml	Anti-dsDNA ug/ml	Total (g) mg/ml	PU	11-20-86 HRI ug/ml	Anti-MRI ug/ml	Anti-ssDNA ug/ml	Anti-dsDNA ug/ml
4	ND	ND	2.4(0.5)	0	0.14 (0.00)	-	-	-	-	-	-	-	-	-	-	-
4	ND	ND	0.8(0.7)	0.3(0.1)	1.2 (0.1)	4	ND	ND	-	-	1.2 (0.1)	-	-	-	-	-
4	ND	ND	0.3(0.1)	0.1(0.1)	0.6 (0.1)	4	ND	ND	-	-	0.7 (0.0)	4	ND	ND	-	-
1	15.7 (1.5)	ND	2.7(0.5)	0	0.5 (0.1)	1	22.8 (9)	0	1.8 (0)	1.7 (0.2)	1.4 (0.4)	1	34.5 (2.7)	0	0	0
1.5	22 (9)	ND	2.0(0.2)	0	0.5 (0.1)	1.5	24 (6)	0	0	0.4 (0.07)	0.7 (0.0)	1.5	47.2 (2.5)	0	0	0
3	24 (0.5)	0	2.0(0.1)	1.5(0.1)	0.6 (0.0)	3	0	0.3(0.5)	0.5 (0)	0.7 (0.2)	1.4 (0.4)	3	31.6 (6.2)	0	0.5 (0.2)	0
2	26.1 (2.5)	0	0	0	0.8 (0.0)	1	0.6 (0.4)	0.05(0.002)	1.8 (0)	1 (0.1)	1.4 (0.4)	1	10.2 (0.9)	0	0	0
1	27.4 (2.9)	0	2.7(0.4)	0	1.9 (0.5)	1	5.9 (0.6)	0.05(0.003)	2.8 (0.9)	2.9 (0.2)	1.3 (0.3)	1	40.8 (7.2)	0	0	0
2	51.5 (4.4)	ND	0	0	0.6 (0.1)	2	22.6 (4)	0	0	0	0.8 (0.1)	1	71 (4.5)	0	0	0
1.5	28 (9)	0	3.6(1.2)	0	1.1 (0.1)	1.5	4.9 (0.5)	0	0	0	-	1.5	55.5 (7.7)	0	0	0

Figure 6

[illegible]

Figure 7

		PRE 10-14-96		11/25/96			
X	PU	Anti-SSDNA ug/ml	Anti-DSDNA ug/ml	PU	Anti-SSDNA ug/ml	Anti-DSDNA ug/ml	Total Ig mg/ml
AR	1	4.2(1.2)	0	2	64.8 (3.3)	24.8 (1)	1.7 (0.08)
AL	1	2.5(0.3)	0.2(0.0)	2	107.6 (4.2)	11.3 (1)	1.8 (0.1)
AM	1	5.1(0.7)	4.2(0.5)	4	0	0	0.2 (0.01)
ALR	1r	0.3(0.1)	0	1	40.9 (1.5)	23 (1.5)	1.8 (0.04)
BR	2	49.0(3.5)	3.3(0.1)	3	10.8 (1.6)	3.9 (0.4)	5.1 (0.1)
BL	1	3.8(1.0)	0	3	4.7 (0.2)	3.1 (0.1)	2.1 (0.03)
BN	1r	5.1(0.02)	0	1	26.8 (3.8)	15.9 (2.6)	7.4 (0.8)
BLR	1	3.0(0.3)	0	1	22.1 (3.2)	23.1 (0.4)	5.9 (0.6)
CR	1	17.6(2.8)	6.7(0.5)	1	124 (0)	0	2.7 (0.04)
CL	1	0	18.9(2.2)	1	140 (23)	66.7 (5.6)	2.8 (0.1)
CN	1	1.03(0.3)	0.6(0.10)	1	0	0	1.3 (0.1)
CLR	1r	22.6(2.08)	7.7(1.06)	0.5	18.6 (1.6)	6.1 (0.3)	1.5 (0.1)
CR	3	0	0	4	70.3 (7.5)	0	0.9 (0.03)
CL	1	4.3(0.6)	3.6(0.6)	1	8.4 (0.1)	0	2.2 (0.2)
CN	1r	5.1(1.1)	8.6(0.1)	0.5	42.5 (4.6)	0	
CLR	1r	0	0	0.5	0	0	

Figure 8

	10-1	10-2	10-3	10-4	10-5	10-6	10-7	10-8	10-9	10-10	10-11	10-12	10-13	10-14	10-15	10-16	10-17	10-18	10-19	10-20	10-21	10-22	10-23	10-24	10-25	10-26	10-27	10-28	10-29	10-30	10-31	10-32	10-33	10-34	10-35	10-36	10-37	10-38	10-39	10-40	10-41	10-42	10-43	10-44	10-45	10-46	10-47	10-48	10-49	10-50	10-51	10-52	10-53	10-54	10-55	10-56	10-57	10-58	10-59	10-60	10-61	10-62	10-63	10-64	10-65	10-66	10-67	10-68	10-69	10-70	10-71	10-72	10-73	10-74	10-75	10-76	10-77	10-78	10-79	10-80	10-81	10-82	10-83	10-84	10-85	10-86	10-87	10-88	10-89	10-90	10-91	10-92	10-93	10-94	10-95	10-96	10-97	10-98	10-99	10-100	10-101	10-102	10-103	10-104	10-105	10-106	10-107	10-108	10-109	10-110	10-111	10-112	10-113	10-114	10-115	10-116	10-117	10-118	10-119	10-120	10-121	10-122	10-123	10-124	10-125	10-126	10-127	10-128	10-129	10-130	10-131	10-132	10-133	10-134	10-135	10-136	10-137	10-138	10-139	10-140	10-141	10-142	10-143	10-144	10-145	10-146	10-147	10-148	10-149	10-150	10-151	10-152	10-153	10-154	10-155	10-156	10-157	10-158	10-159	10-160	10-161	10-162	10-163	10-164	10-165	10-166	10-167	10-168	10-169	10-170	10-171	10-172	10-173	10-174	10-175	10-176	10-177	10-178	10-179	10-180	10-181	10-182	10-183	10-184	10-185	10-186	10-187	10-188	10-189	10-190	10-191	10-192	10-193	10-194	10-195	10-196	10-197	10-198	10-199	10-200	10-201	10-202	10-203	10-204	10-205	10-206	10-207	10-208	10-209	10-210	10-211	10-212	10-213	10-214	10-215	10-216	10-217	10-218	10-219	10-220	10-221	10-222	10-223	10-224	10-225	10-226	10-227	10-228	10-229	10-230	10-231	10-232	10-233	10-234	10-235	10-236	10-237	10-238	10-239	10-240	10-241	10-242	10-243	10-244	10-245	10-246	10-247	10-248	10-249	10-250	10-251	10-252	10-253	10-254	10-255	10-256	10-257	10-258	10-259	10-260	10-261	10-262	10-263	10-264	10-265	10-266	10-267	10-268	10-269	10-270	10-271	10-272	10-273	10-274	10-275	10-276	10-277	10-278	10-279	10-280	10-281	10-282	10-283	10-284	10-285	10-286	10-287	10-288	10-289	10-290	10-291	10-292	10-293	10-294	10-295	10-296	10-297	10-298	10-299	10-300	10-301	10-302	10-303	10-304	10-305	10-306	10-307	10-308	10-309	10-310	10-311	10-312	10-313	10-314	10-315	10-316	10-317	10-318	10-319	10-320	10-321	10-322	10-323	10-324	10-325	10-326	10-327	10-328	10-329	10-330	10-331	10-332	10-333	10-334	10-335	10-336	10-337	10-338	10-339	10-340	10-341	10-342	10-343	10-344	10-345	10-346	10-347	10-348	10-349	10-350	10-351	10-352	10-353	10-354	10-355	10-356	10-357	10-358	10-359	10-360	10-361	10-362	10-363	10-364	10-365	10-366	10-367	10-368	10-369	10-370	10-371	10-372	10-373	10-374	10-375	10-376	10-377	10-378	10-379	10-380	10-381
--	------	------	------	------	------	------	------	------	------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	-------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------

Figure 9

[illegible]

Figure 20

STUDY NO.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100	101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	116	117	118	119	120	121	122	123	124	125	126	127	128	129	130	131	132	133	134	135	136	137	138	139	140	141	142	143	144	145	146	147	148	149	150	151	152	153	154	155	156	157	158	159	160	161	162	163	164	165	166	167	168	169	170	171	172	173	174	175	176	177	178	179	180	181	182	183	184	185	186	187	188	189	190	191	192	193	194	195	196	197	198	199	200	201	202	203	204	205	206	207	208	209	210	211	212	213	214	215	216	217	218	219	220	221	222	223	224	225	226	227	228	229	230	231	232	233	234	235	236	237	238	239	240	241	242	243	244	245	246	247	248	249	250	251	252	253	254	255	256	257	258	259	260	261	262	263	264	265	266	267	268	269	270	271	272	273	274	275	276	277	278	279	280	281	282	283	284	285	286	287	288	289	290	291	292	293	294	295	296	297	298	299	300	301	302	303	304	305	306	307	308	309	310	311	312	313	314	315	316	317	318	319	320	321	322	323	324	325	326	327	328	329	330	331	332	333	334	335	336	337	338	339	340	341	342	343	344	345	346	347	348	349	350	351	352	353	354	355	356	357	358	359	360	361	362	363	364	365	366	367	368	369	370	371	372	373	374	375	376	377	378	379	380	381	382	383	384	385	386	387	388	389	390	391	392	393	394	395	396	397	398	399	400	401	402	403	404	405	406	407	408	409	410	411	412	413	414	415	416	417	418	419	420	421	422	423	424	425	426	427	428	429	430	431	432	433	434	435	436	437	438	439	440	441	442	443	444	445	446	447	448	449	450	451	452	453	454	455	456	457	458	459	460	461	462	463	464	465	466	467	468	469	470	471	472	473	474	475	476	477	478	479	480	481	482	483	484	485	486	487	488	489	490	491	492	493	494	495	496	497	498	499	500	501	502	503	504	505	506	507	508	509	510	511	512	513	514	515	516	517	518	519	520	521	522	523	524	525	526	527	528	529	530	531	532	533	534	535	536	537	538	539	540	541	542	543	544	545	546	547	548	549	550	551	552	553	554	555	556	557	558	559	560	561	562	563	564	565	566	567	568	569	570	571	572	573	574	575	576	577	578	579	580	581	582	583	584	585	586	587	588	589	590	591	592	593	594	595	596	597	598	599	600	601	602	603	604	605	606	607	608	609	610	611	612	613	614	615	616	617	618	619	620	621	622	623	624	625	626	627	628	629	630	631	632	633	634	635	636	637	638	639	640	641	642	643	644	645	646	647	648	649	650	651	652	653	654	655	656	657	658	659	660	661	662	663	664	665	666	667	668	669	670	671	672	673	674	675	676	677	678	679	680	681	682	683	684	685	686	687	688	689	690	691	692	693	694	695	696	697	698	699	700	701	702	703	704	705	706	707	708	709	710	711	712	713	714	715	716	717	718	719	720	721	722	723	724	725	726	727	728	729	730	731	732	733	734	735	736	737	738	739	740	741	742	743	744	745	746	747	748	749	750	751	752	753	754	755	756	757	758	759	760	761	762	763	764	765	766	767	768	769	770	771	772	773	774	775	776	777	778	779	780	781	782	783	784	785	786	787	788	789	790	791	792	793	794	795	796	797	798	799	800	801	802	803	804	805	806	807	808	809	810	811	812	813	814	815	816	817	818	819	820	821	822	823	824	825	826	827	828	829	830	831	832	833	834	835	836	837	838	839	840	841	842	843	844	845	846	847	848	849	850	851	852	853	854	855	856	857	858	859	860	861	862	863	864	865	866	867	868	869	870	871	872	873	874	875	876	877	878	879	880	881	882	883	884	885	886	887	888	889	890	891	892	893	894	895	896	897	898	899	900	901	902	903	904	905	906	907	908	909	910	911	912	913	914	915	916	917	918	919	920	921	922	923	924	925	926	927	928	929	930	931	932	933	934	935	936	937	938	939	940	941	942	943	944	945	946	947	948	949	950	951	952	953	954	955	956	957	958	959	960	961	962	963	964	965	966	967	968	969	970	971	972	973	974	975	976	977	978	979	980	981	982	983	984	985	986	987	988	989	990	991	992	993	994	995	996	997	998	999	1000	1001	1002	1003	1004	1005	1006	1007	1008	1009	1010	1011	1012	1013	1014	1015	1016	1017	1018	1019	1020	1021	1022	1023	1024	1025	1026	1027	1028	1029	1030	1031	1032	1033	1034	1035	1036	1037	1038	1039	1040	1041	1042	1043	1044	1045	1046	1047	1048	1049	1050	1051	1052	1053	1054	1055	1056	1057	1058	1059	1060	1061	1062	1063	1064	1065	1066	1067	1068	1069	1070	1071	1072	1073	1074	1075	1076	1077	1078	1079	1080	1081	1082	1083	1084	1085	1086	1087	1088	1089	1090	1091	1092	1093	1094	1095	1096	1097	1098	1099	1100	1101	1102	1103	1104	1105	1106	1107	1108	1109	1110	1111	1112	1113	1114	1115	1116	1117	1118	1119	1120	1121	1122	1123	1124	1125	1126	1127	1128	1129	1130	1131	1132	1133	1134	1135	1136	1137	1138	1139	1140	1141	1142	1143	1144	1145	1146	1147	1148	1149	1150	1151	1152	1153	1154	1155	1156	1157	1158	1159	1160	1161	1162	1163	1164	1165	1166	1167	1168	1169	1170	1171	1172	1173	1174	1175	1176	1177	1178	1179	1180	1181	1182	1183	1184	1185	1186	1187	1188	1189	1190	1191	1192	1193	1194	1195	1196	1197	1198	1199	1200	1201	1202	1203	1204	1205	1206	1207	1208	1209	1210	1211	1212	1213	1214	1215	1216	1217	1218	1219	1220	1221	1222	1223	1224	1225	1226	1227	1228	1229	1230	1231	1232	1233	1234	1235	1236	1237	1238	1239	1240	1241	1242	1243	1244	1245	1246	1247	1248	1249	1250	1251	1252	1253	1254	1255	1256	1257	1258	1259	1260	1261	1262	1263	1264	1265	1266	1267	1268	1269	1270	1271	1272	1273	1274	1275	1276	1277	1278	1279	1280	1281	1282	1283	1284	1285	1286	1287	1288	1289	1290	1291	1292	1293	1294	1295	1296	1297	1298	1299	1300	1301	1302	1303	1304	1305	1306	1307	1308	1309	1310	1311	1312	1313	1314	1315	1316	1317	1318	1319	1320	1321	1322	1323	1324	1325	1326	1327	1328	1329	1330	1331	1332	1333	1334	1335	1336	1337	1338	1339	1340	1341	1342	1343	1344	1345	1346	1347	1348	1349	1350	1351	1352	1353	1354	1355	1356	1357	1358	1359	1360	1361	1362	1363	1364	1365	1366	1367	1368	1369	1370	1371	1372	1373	1374	1375	1376	1377	1378	1379	1380	1381	1382	1383	1384	1385	1386	1387	1388	1389	1390	1391	1392	1393	1394	1395	1396	1397	1398	1399	1400	1401	1402	1403	1404	1405	1406	1407	1408	1409	1410	1411	1412	1413	1414	1415	1416	1417	1418	1419	1420	1421	1422	1423	1424	1425	1426	1427	1428	1429	1430	1431	1432	1433	1434	1435	1436	1437	1438	1439	1440	1441	1442	1443	1444	1445	1446	1447	1448	1449	1450	1451	1452	1453	1454	1455	1456	1457	1458	1459	1460	1461	1462	1463	1464	1465	1466	1467	1468	1469	1470	1471	1472	1473	1474	1475	1476	1477	1478	1479	
-----------	---	---	---	---	---	---	---	---	---	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	--